PI-123

PHARMACOKINETIC INTERACTION BETWEEN VORICONAZOLE AND RITONAVIR AT STEADY STATE IN HEALTHY SUBJECTS. P. Liu, PhD, G. Foster, PhD, R. Labadie, MPH, M. J. Allison, MD, A. Sharma, PhD, Pfizer Inc, MDS Pharma Services, Groton, CT.

AIM: Voriconazole (VORI), a triazole antifungal agent, is metabolized by the cytochrome P450 CYP2C19, CYP2C9, and to a lesser extent by CYP3A4. Ritonavir (RITO), a protease inhibitor, is primarily metabolized by the CYP3A4. This study was conducted to evaluate the pharmacokinetic interactions between these two compounds.

METHODS: A randomized, subject and investigator blinded with respect to VORI, placebo controlled (VORI only), parallel group, two-period multiple-dose study was conducted in 34 healthy male subjects. In Period 1, subjects received therapeutic doses of VORI (400 mg twice daily (BID) on day 1 followed by 200 mg BID) or placebo for 3 days. After a 7-day washout, subjects received 400 mg BID RITO for 20 days in Period 2. After 10 days of RITO alone, therapeutic dose of VORI or placebo were co-administered for the next 10 days. The steady state pharmacokinetics of VORI and RITO following 10 days of co-administration were compared to those of VORI alone and RITO alone, respectively.

RESULTS: RITO decreased the mean steady state area under the concentration-time curve from time 0 to tau (AUC_{0-12}) of VORI by 82% (26500 vs. 4250 ng·hr/mL, $P < 0.001$), and the mean steady state peak plasma concentration (C_{max}) of VORI by 66% (3600 vs. 1220 ng/mL, $P < 0.001$). VORI had no effect on the steady state RITO pharmacokinetics.

CONCLUSIONS: Co-administration of VORI with RITO should be contraindicated due to the clinically significant effect of RITO on VORI pharmacokinetics.

PI-124

PHARMACOKINETIC INTERACTION BETWEEN VORICONAZOLE AND EFAVIRENZ AT STEADY STATE IN HEALTHY SUBJECTS. P. Liu, PhD, G. Foster, PhD, R. Labadie, MPH, M. J. Gutierrez, MD, A. Sharma, PhD, Pfizer Inc, CNS Neurosciences, Inc., Groton, CT.

AIM: Voriconazole (VORI), a triazole antifungal agent, is metabolized by the cytochrome P450 CYP2C19, CYP2C9 and to a lesser extent by CYP3A4. Efavirenz (EFAV), a reverse transcriptase inhibitor, is primarily metabolized by the CYP3A4. This study was conducted to evaluate the pharmacokinetic interactions between these two compounds.

METHODS: A randomized, subject and investigator blinded with respect to VORI, placebo controlled, parallel two-period multiple-dose study was conducted in 34 healthy male subjects. In Period 1, subjects received therapeutic doses of VORI (400 mg twice daily (BID) on day 1 followed by 200 mg BID) or placebo for 3 days. After a 7-day washout, subjects received 400 mg once daily (QD) EFAV for 19 days in Period 2. After 10 days of EFAV alone, therapeutic doses of VORI or placebo were co-administered for the next 9 days. The steady state pharmacokinetics of VORI and EFAV following 9 days of co-administration were compared to those of VORI alone and EFAV alone.

RESULTS: EFAV decreased the mean steady state area under the concentration-time curve from time 0 to tau (AUC_{0-12}) of VORI by 77% (26300 vs. 5710 ng·hr/mL, $P < 0.001$), and peak plasma concentration (C_{max}) of VORI by 61% (3060 vs. 1150 ng/mL, $P < 0.001$). While VORI increased the mean steady state AUC_{0-24} and C_{max} of EFAV by 44% and 38%, respectively.

CONCLUSIONS: Co-administration of VORI with EFAV should be contraindicated due to the clinically significant effect of EFAV on VORI pharmacokinetics.

PI-125

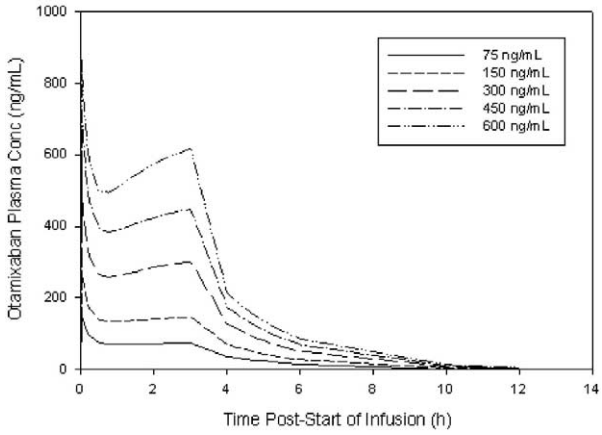
PROSPECTIVE DOSE PREDICTION FOR FXA INHIBITOR OTAMIXABAN (OTAM) USING PK/PD SIMULATIONS ACCOUNTING FOR NON-DOSE PROPORTIONAL PLASMA EXPOSURE. A. J. Paccaly, PharmD, A. Frick, PhD, S. Rohatagi, PhD, Sanofi-Aventis, Bridgewater, NJ.

BACKGROUND/AIMS: OTAM is a direct and selective FXa inhibitor under development for treatment of Acute Coronary Syndrome (ACS). This work describes PK/PD modeling and simulations to predict doses for dose-ranging Phase II study with target C_{eoi} of 75 to 600 ng/mL (MTD).

METHODS: Plasma concentrations-time data from 3 Phase I/II studies were fitted simultaneously to a two-compartment model using WINNONLIN. The change in plasma clearance and volume of distribution with dose was accounted by introducing a linear equation for the change in volume of distribution as a function of the infusion rate. Furthermore, because a linear relationship exists between PK and PD clotting time markers (aPTT, PT, and RVVT), PK concentrations were sufficient to predict PD.

RESULTS: Simulated mean concentrations were well separated for each dose. The combined 1 min/3 h infusions allowed target C_{eoi} to be reached immediately, with a "dip" not exceeding 20% of C_{eoi}.

CONCLUSIONS: Predictable PK/PD model allowed for optimal dose selection for the Phase II study.



Target Plasma Concentration		Dosage		Predicted Plasma Concentration at Time Post- start of Infusion (ng/mL)					
ng/mL	Group	Bolus mg/kg	Infusion mg/kg/h	1 min	10 min	0.75 h	3 h	4 h	5 h
75	1	0.025	0.035	153	106	71	75	38	24
150	2	0.045	0.065	275	193	133	146	70	44
300	3	0.080	0.120	481	361	256	301	127	80
450	4	0.120	0.160	736	526	383	448	174	110
600	5	0.140	0.200	861	632	494	617	215	135